

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/B2004/000899

International filing date (day/month/year)
25.03.2004

Priority date (day/month/year)
27.03.2003

International Patent Classification (IPC) or both national classification and IPC
A61K31/4415, A61K31/4355, A61K31/675, A61P39/00

Applicant
MEDICURE, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No.
PCT/IB2004/000899

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IB2004/000899

Box No. II Priority

1. ☒ The following document has not been furnished:

☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IB2004/000899

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 1-49

because:

- ☒ the said international application, or the said claims Nos. 1 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos. 1 (partially) 2-49
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IB2004/000899

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:
- ☐ paid additional fees.
 - ☐ paid additional fees under protest.
 - ☒ not paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1 (partially)

Box No. V Reasoned statement under Rule 43b/s.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	
	No: Claims	1
Inventive step (IS)	Yes: Claims	
	No: Claims	1
Industrial applicability (IA)	Yes: Claims	see separate sheet
	No: Claims	

2. Citations and explanations

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IB2004/000899

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Re Item III.

Claim 1 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Present claim 1 relate to a method defined by reference to the following parameters: modulation of cell death.

The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to the therapeutic use of pyridoxal-5'-phosphate.

No Written Opinion will be formulated with respect to subject matter which is not covered by the search report.

Re Item IV.

The separate inventions/groups of inventions are:

1. Claim 1 (partially)

Use of pyridoxal-5'-phosphate for modulating cell death.

2. Claim 1 (partially)

Use of pyridoxic acid for modulating cell death.

3. Claim 1 (partially)

Use of pyridoxal for modulating cell death.

4. Claim 1 (partially)

Use of pyridoxine for modulating cell death.

5. Claim 1 (partially)

Use of pyridoxamine for modulating cell death.

6. Claims 2-10

Use of a compound of the formula of claim 2 for modulating cell death.

7. Claims 11-25

Use of a compound of the formula of claim 11 for modulating cell death.

8. Claims 26-33

Use of a compound of the formula of claim 26 for modulating cell death.

9. Claims 34-40

Use of a compound of the formula of claim 34 for modulating cell death.

10. Claims 41-49

Use of a compound of the formula of claim 49 for modulating cell death.

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

The problem to be solved by the present application is to provide for modulating cell death and in particular cell death associated with disease states such as diabetes, pancreatitis, liver damage, leaky gout syndrome, Parkinson's disease, Alzheimer's disease, Multiple Sclerosis, arteriosclerosis, intermittent claudication, peripheral vascular disease, asthma, emphysema, chronic pulmonary disease, cataracts, retinopathy, macular degeneration, rheumatoid arthritis, glomerulonephritis, age spots, vitiligo, accelerated aging, cancer, autoimmune diseases, sepsis, AIDS, inflammatory diseases including Crohn's disease, gout, Hashimoto's thyroiditis, osteoarthritis, pemphigus, periodic fever syndromes, psoriasis, sarcoidosis, systemic lupus erythematosus, ulcerative colitis, vasculitides, and xenograft rejection and also inflammatory disorders (e.g. septic shock) of infectious origin and other disease states as specified on page 3 and 4 of the description.

The proposed solutions are to use pyridoxal-5'-phosphate, pyridoxic acid, pyridoxal, pyridoxine, pyridoxamine, a compound of the formula of claim 2, a compound of the formula of claim 11, a compound of the formula of claim 26, a compound of the formula of claim 34, a compound of the formula of claim 41.

WO0057863 discloses the use of pyridoxal-5'-phosphate, pyridoxine, pyridoxal and pyridoxamine to decrease the mortality and increase the survival after myocardial infarction, i.e. a modulation of cell death. See the passages cited in the search report.

WO0103682 discloses the use of pyridoxal-5'-phosphate, pyridoxamine, pyridoxal, pyridoxine, 3-acylated pyridoxal analog and/or acid addition salts of these in relation to the treatment of diabetes mellitus, hyperinsulinemia, diabetes-induced hypertension, or diabetes-related damage. See the passages cited in the search report.

EP282696 discloses the use of pyridoxal; pyridoxal phosphate; pyridoxamine and/or

pyridoxamine phosphate for preventing or treating hyperlipidaemia and atherosclerosis. See the passages cited in the search report.

US6339085 discloses the use of compounds of the formula of claim 2 in the treatment of hypertension, myocardial infarction, ischemia reperfusion injury (including apoptosis), congestive heart failure, arrhythmia, blood coagulation, hypertrophy, deep vein thrombosis, disseminated intravascular coagulopathy, pulmonary embolism and platelet aggregation, and melanoma. See the passages cited in the search report.

WO9832429 discloses the use of pyridoxal phosphate in the treatment of psoriasis. See claim 1,6,12.

SU1808326 discloses the use of pyridoxal phosphate in the treatment of acute pancreatitis. See the abstract.

WO0164692 discloses the use of compounds of the formulae of claims 26 and 34 for the treatment of diabetes. See the passages cited in the search report.

WO0053606 discloses the use of compounds of the formulae of claims 2 and 11 for the treatment of cardiovascular disorders, septic shock, septicemia, cancer, atherosclerosis. See the passages cited in the search report.

According to Article 3(4)(iii) PCT, an international application shall comply with "the prescribed requirement of unity of invention". This means, as explained in Rule 13.1 PCT, that the application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept.

From the above cited documents, it appears that the use the compounds of the present invention in relation to above specified conditions is known in the prior art and can not fulfil the role of special technical feature (general inventive concept) in the sense of Rule 13.2 PCT.

Accordingly there is no new technical effect linking the different groups of inventions.

In the present application no further technical feature can be distinguished that can be regarded as a "special technical feature" involved in the technical relationship among the different inventions.

Consequently the present application lacks unity of invention.

As searching the other inventions would have caused a major additional searching effort, only the first invention was searched.

The application relates to a plurality of inventions, or groups of inventions, in the sense of Rule 13.1 PCT. They have been divided as defined above. If the applicant pays additional fees for one (or more) not yet searched group(s) of invention(s), then the further search(es) may reveal further prior art that gives evidence of a further lack of unity 'a posteriori' within one (or more) of the not yet searched group(s). In such a case only the first invention in this (each of these) group(s) of inventions, which is considered to lack unity of invention, will be the subject of a search.

Re Item V.

1. The attention of the Applicant is drawn to the fact that present opinion regarding novelty, inventive step and industrial applicability is only established with regard to subject matter for which an international search report has been established i.e. the use of pyridoxal-5'-phosphate in therapy.
2. The following documents are referred to in this communication:
 - D1 : WO 00/57863 A (UNIV MANITOBA ; MEDICURE INC (CA)) 5 October 2000 (2000-10-05)
 - D2 : WO 01/03682 A (MEDICURE INC) 18 January 2001 (2001-01-18)
 - D3 : EP 0 282 696 A (SPECK ULRICH) 21 September 1988 (1988-09-21)
 - D4 : US 6 339 085 B1 (HAQUE WASIMUL ET AL) 15 January 2002 (2002-01-15)
 - D5 : WO 98/32429 A (GALLAGHER JAMES ANTHONY ; UNIV LIVERPOOL (GB); BOWLER WAYNE BARRY (GB)) 30 July 1998 (1998-07-30)
 - D6 : DATABASE WPI Section Ch, Week 199425
Derwent Publications Ltd., London, GB; Class B05, AN 1994-207332
XP002291398 & ; SU 1 808 326 A1 (RYAZAN MED
INST) 15 April 1993 (1993-04-15)
 - D7 : WO 01/64692 A (MEDICURE INTERNAT INC) 7 September 2001 (2001-09-07)
 - D8 : WO 00/53606 A (MEDICURE INC) 14 September 2000 (2000-09-14)

- D9 : GENG M Y ET AL: "Protective effects of pyridoxal phosphate against glucose deprivation-induced damage in cultured hippocampal neurons." JOURNAL OF NEUROCHEMISTRY. JUN 1997, vol. 68, no. 6, June 1997 (1997-06), pages 2500-2506, XP001197371 ISSN: 0022-3042
- D10 : DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SAWAKI, SHUNJI ET AL: "Effect of pyridoxal phosphate administration on hepatitis C virus RNA in patients with hepatitis type C" XP002291396
retrieved from STN Database accession no. 1997:732628
- D11 : DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SAWAKI, SHUNJI ET AL: "Effect of pyridoxal phosphate on the CD4, CD8 T cell and HCV-RNA in patients with hepatitis type C" XP002291397
retrieved from STN Database accession no. 1998:406378
- D12 : DATABASE WPI Section Ch, Week 199748
Derwent Publications Ltd., London, GB; Class B03, AN 1997-516155 XP002291399 & JP 09 221425 A (TAIHO PHARM CO LTD) 26 August 1997 (1997-08-26)
- D13 : YAMASHIMA, T. ET AL: "Neuroprotective effects of pyridoxal phosphate and pyridoxal against ischemia in monkeys" NUTRITIONAL NEUROSCIENCE , 4(5), 389-397 CODEN: NNINFE; ISSN: 1028-415X, 2001, XP008033483
- D14 : EP 0 379 936 A (VESTA MED PTY LTD) 1 August 1990 (1990-08-01)
- D15 : ISHAQUE A ET AL: "Role of vitamins in determining apoptosis and extent of suppression by bcl-2 during hybridoma cell culture" APOPTOSIS, vol. 7, no. 3, June 2002 (2002-06), pages 231-239, XP008033442 ISSN: 1360-8185

2 INDEPENDENT CLAIM 1

- 2.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT. Document D1 discloses (see the passages cited in the search report) the use of

pyridoxal-5'-phosphate, pyridoxine, pyridoxal and pyridoxamine to decrease the mortality and increase the survival after myocardial infarction. Consequently, the subject matter of claim 1 is not novel over D1.

- 2.2 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT. Document D2 discloses (see the passages cited in the search report) the treatment of diabetes mellitus, hyperinsulinemia, diabetes-induced hypertension, or diabetes-related damage to e.g. blood vessels and eyes in mammal comprising administering pyridoxal-5'-phosphate, pyridoxamine, pyridoxal or pyridoxine. Consequently, the subject matter of claim 1 is not novel over D2.
- 2.3 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT. Document D3 discloses (see the passages cited in the search report) the use of pyridoxine derivs. (A), or their salts, including pyridoxal-5-phosphate, for preventing or treating hyperlipidaemia and atherosclerosis. Consequently, the subject matter of claim 1 is not novel over D3.
- 2.4 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT. Document D5 discloses (see the passages cited in the search report) pyridoxal phosphate useful in medicaments for skin conditions characterised by keloid formation, dermatitis and psoriasis. Consequently, the subject matter of claim 1 is not novel over D5.
- 2.5 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT. Document D6 discloses the use of pyridoxal phosphate in the treatment of acute pancreatitis. See the abstract. Consequently, the subject matter of claim 1 is not novel over D6.
- 2.6 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT. Document D9 discloses (see the passages cited in the search report) the protective effects of pyridoxal phosphate against glucose deprivation-induced damage in cultured hippocampal neurons, which has been demonstrated to be

related to normal aging but also to Parkinson's and Alzheimer's diseases.
Consequently, the subject matter of claim 1 is not novel over D9.

- 2.7 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT. Document D10 discloses (see the passages cited in the search report) the therapeutic effects of pyridoxal phosphate (PP) and the clinical improvement in twenty patients with hepatitis type C. During the PP treatment, the amt. of HCV tended to decrease. Consequently, the subject matter of claim 1 is not novel over D10.
- 2.8 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT. Document D11 discloses (see the passages cited in the search report) that Pyridoxal phosphate (PP) was administered to 32 patients with hepatitis type C at 30 mg/day for about 1 mo orally. To the inpatients, i.v. injection of PP (30 mg/day) was simultaneously added to the oral administration. Nos. of CD4 and CD8 T cells were measured using a flow cytometer and hepatitis C virus (HCV)-RNA was detd. by PCR method. After treatment, the CD4/CD8 ratio and HCV-RNA tended to increase and decrease, resp. The possibility of PP application to AIDS was discussed. Consequently, the subject matter of claim 1 is not novel over D11.
- 2.9 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT. Document D12 discloses (see the passages cited in the search report) the use of a thiol protease inhibitor, preferably vitamin B6 (pyridoxal, pyridoxal phosphate or pyridoxamine) to treat myodystrophy, amyotrophy, myocardial infarction, cerebral apoplexy, Alzheimer's disease, consciousness hindrance and dyskinesia in injury of head, multiple sclerosis, neuropathy of peripheral nervous system, cataract, inflammation, allergy, fulminant hepatitis, osteoporosis, hypercalcaemia, breast cancer, prostatic cancer, prostatomegaly, inhibition to platelet aggregation. Consequently, the subject matter of claim 1 is not novel over D12.
- 2.10 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT. Document D13 discloses (see the passages cited in the search report) the neuroprotective effects of pyridoxal phosphate and pyridoxal against ischemia in

monkeys. Consequently, the subject matter of claim 1 is not novel over D13.

- 2.11 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT. Document D14 discloses (see the passages cited in the search report) the use of pyridoxal (PL) or its prodrugs including pyridoxal phosphate in the form of pharmaceutical or dietary compsns. for the treatment of/or prophylaxis of diseases including microbial infections causing erythrocyte destruction, e.g. malaria, bartonellosis, Rift Valley fever, corridor disease and biliary fever. Consequently, the subject matter of claim 1 is not novel over D14.
- 2.12 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT. Document D15 discloses (see the passages cited in the search report) the role of vitamins including pyridoxine in determining apoptosis and extent of suppression by bcl-2 during hybridoma cell culture. Consequently, the subject matter of claim 1 is not novel over D15.